

MARKED-UP VERSION OF AMENDMENTS

The title has been amended to read as follows:

~~ADSORBENT FOR TRANSFORMING GROWTH FACTOR- $\beta$ , METHOD FOR REMOVING  
THE TRANSFORMING GROWTH FACTOR- $\beta$  BY ADSORPTION AND ADSORBER  
PACKED WITH ADSORBENT~~

Claims 1 and 5 have been canceled.

Claim 2-4 has been amended as follows:

2. (Amended) The ~~adsorbent~~ method of Claim ~~1~~ 4, wherein said water-insoluble carrier is a water-insoluble porous carrier.

3. (Amended) The ~~adsorbent~~ method of Claim ~~2~~ 4, wherein said water-insoluble porous carrier has an exclusion limit for globular protein of 5,000 to 600,000.

4. (Amended) A method for removing a transforming growth factor- $\beta$  from a body fluid, which comprises bringing a body fluid into contact with an adsorbent comprising (i) a water-insoluble carrier, and (ii) a compound immobilized on said carrier and having a log P value of at least 2.50 wherein P is a partition coefficient in an octanol-water system, said body fluid being a member selected from the group consisting of plasma, serum, ascites, lymph and synovia.

REMARKS

By the present amendment, non-elected claims 1 and 5 have been canceled and claim 4 has been amended. Support for the added language in claim 4 is found in the original application, in particular on page 4, line 16. Claims 2-3 have been amended to depend on claim 4 and the title has been amended accordingly. Consideration of claims 2-3 as dependent of claim 4 is respectfully requested.

In the Office Action, claim 4 is rejected under 35 U.S.C. 103(a) as obvious over either of US 4774322 (Seyedin et al.), US 4931548 (Lucas) or US 5322933 (Davies), in view of US 6270994 (Miyazono). It is alleged in the Office Action that each of the first three references discloses isolating TGF- $\beta$  using reverse-phase chromatography with a C-18 column, and that the fourth cited reference discloses the presence of TGF- $\beta$  in body fluid associated with many conditions, so that it would have been obvious to remove TGF- $\beta$  from body fluid with a C-18 column chromatography.

Reconsideration and withdrawal of the rejection is respectfully requested. Seyedin, Lucas and Davies disclose methods for removing a TGF- $\beta$  from particular prepared fractions, namely, bone in Seyedin, platelets in Lucas, and a medium conditioned by culture of Chinese hamster ovary cell line in Davies. However, body fluids contain many kinds of components and are very different from the prepared fractions in these three references, which were used to isolate TGF- $\beta$  for research purposes. As a result, these references do not provide any motivation to isolate TGF-

$\beta$  from body fluids, nor any suggestion that removal of TGF- $\beta$  from body fluids would be successful.

Further, Miyazono discloses that TGF- $\beta$  is abnormally elevated in liver, kidney, or lungs, among others, in patients with fibrosis, and indicates that Smad 6 can be used to reduce the TGF- $\beta$  activity. However, Miyazono is completely silent as to removing TGF- $\beta$  from body fluids.

In contrast, the present inventors have discovered that TGF- $\beta$  can be removed from body fluid selected from the group consisting of plasma, serum, ascites, lymph and synovia by contacting the body fluid with an adsorbent as recited in present claim 4. This method makes it possible to reduce TGF- $\beta$  levels very effectively. The body fluids which are contacted with the adsorbent in the presently claimed invention are very different from the pre-treated fractions of the three first cited references, and neither these three references nor Miyazono provides a suggestion that removal of TGF- $\beta$  from body fluids such as plasma, serum, ascites, lymph and synovia would be successful. Therefore, the presently claimed method is not obvious over the cited references taken alone or in any combination.

In view of the above, it is submitted that the rejection should be withdrawn.

In conclusion, the invention as presently claimed is patentable. It is believed that the claims are in allowable condition and a notice to that effect is earnestly requested.

In the event there is, in the Examiner's opinion, any outstanding issue and such issue may be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

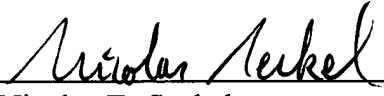
Serial Number: 09/773,598

Group Art Unit: 1646

In the event this paper is not considered to be timely filed, the Applicants hereby petition for an appropriate extension of the response period. Please charge the fee for such extension and any other fees which may be required to our Deposit Account No. 01-2340.

Respectfully submitted,

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